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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,407	03/25/2005	Victor Willem Van Beusechem	253-9	9615

23869 7590 02/05/2010

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
02/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,407	VAN BEUSECHEM ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,15-17,19-23 and 26-41* is/are pending in the application.

4a) Of the above claim(s) *10,15-17 and 19-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/28/2009; 1/4/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/28/2009 and 1/4/2010 has been entered.

Claim Status

Claims 10, 15-17, 19-23 and 26-41 are pending. Claim 41 is newly added. Claims 26, 32-33 and 40 are amended. Claims 1-9, 11-14, 18, and 24-25 have been cancelled. Claims 10, 15-17, and 19-23 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 26-41 are under current examination.

Priority

This application claims benefit from foreign Application No. EP/02075108.7, filed 14 January 2002 and PCT Application No. PCT/EP03/00340, filed 14 January 2003. The instant application has been granted the benefit date, 14 January 2002, from the application EP/02075108.7.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 4 January 2010 and 28 December 2009 consisting of 4 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Sequence Compliance

Claim 40 does not conform to sequence rules, requiring the use of "SEQ ID NO:" See 37 CFR 1.821-1.825.

RESPONSE TO ARGUMENTS

35 USC § 102

The rejection of claims 26-27, 34 and 39 under 35 U.S.C. 102(b) as being anticipated by Fueyo et al (Oncogene. 2000. 19:2-12) and as evidenced by Nevins (Human Molecular Genetics. 2001. 10(7):699-703) is withdrawn in response to the applicant's arguments and/or claim amendments.

The applicant's arguments have been fully considered and are persuasive. The applicant argues "the adenovirus of Fueyo et al. does not include a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway, as required by claim 26." While it is clear from Fueyo that their adenovirus induces apoptosis in p53 deficient cells, it is not clear that Fueyo teaches that the

genome of adenovirus comprises "a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway." While the art is aware that E1A, including the mutant form as taught by Fueyo, induces p53-mediated apoptosis, the examiner does not interpret the adenoviral E1A protein as being a "mammalian restoring factor." While the specification has a broad definition of "restoring factor," and there are numerous genes which could be interpreted as being involved in the p53 apoptosis pathway, the examiner cannot provide evidence that the adenovirus vector of Fueyo satisfies this particular limitation.

The applicant further argues that the adenovirus of Fueyo does not have a genome which comprises p53 or a p53 derivative. The applicant is correct that Fueyo does not state that the genome of their virus comprises p53 or a p53 derivative.

Accordingly, the examiner finds the Fueyo reference deficient in regard to the limitation, "wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway."

Therefore, the examiner hereby withdraws the rejection of claims 26-27, 34 and 39 under 35 U.S.C. 102(b) as being anticipated by Fueyo et al (Oncogene. 2000. 19:2-12) and as evidenced by Nevins (Human Molecular Genetics. 2001. 10(7):699-703).

35 USC § 103

The rejection of claims 26-33 and 35-39 under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (US-6,638,762) in view of Lin et al. (Cancer Research. Oct 15, 2000. 60. p.5895-5901) is withdrawn.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Fueyo & Lin

Claims 26-27 and 30-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fueyo et al (Oncogene. 2000. 19:2-12) in view of Lin et al. (Cancer Research. Oct 15, 2000. 60. p.5895-5901).

Claim 26 is directed to a replication competent recombinant adenovirus, being capable to replicate and having lytic capacity in target cells, wherein said target cells are hampered in a p53 dependent apoptosis pathway, wherein the adenovirus is a conditionally replicating adenovirus; wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells; wherein said coding sequence is operably linked to one or more expression control sequences functional in said target cells, and whereby said restoring factor induces accelerated cell lysis and/or a faster release of virus progeny when compared to a recombinant adenovirus lacking said coding sequence and wherein the virus genome further comprises a gene selected from a gene encoding the adenovirus E1B-19kDa protein or a functional analog or derivative thereof and a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof.

Fueyo et al. teach a “replication competent” recombinant adenovirus (p.2, *Results*, paragraph 1). Further, Fueyo et al. teach that the virus can “replicate in and lyse cancer cells” (abstract) and particularly teach that they have these functions in cells that are hampered in a p53 dependent apoptosis pathway. Specifically, Fueyo teaches “electron microscopy showed necrosis and apoptosis features in the infected calls (data

not shown). Interestingly, Δ24 adenovirus induced cell death even in mutant-p53 cells" (page 7, col.1, *Treatment with Δ24* section). Therefore, Fueyo teaches that their adenovirus induces apoptosis in target cells that are deficient in p53 apoptosis pathway. In addition, there is nothing in Fueyo that indicates their "replication competent" recombinant adenovirus does not contain the adenovirus E1B-19kDa protein and the adenovirus E1B-55kDa protein. Fueyo particularly teaches that only the E1A and E3 proteins are altered in their adenovirus (page 8, col.2, *Construction of the Δ24* section). Therefore, the examiner concludes Fueyo provides an adenovirus having the adenovirus E1B-19kDa protein and the adenovirus E1B-55kDa protein.

The adenovirus of Fueyo et al. does not include a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway, as required by claim 26. While it is clear from Fueyo that their adenovirus induces apoptosis in p53 deficient cells, it is not clear that Fueyo teaches that the genome of adenovirus comprises "a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway." While the art is aware that E1A, including the mutant form as taught by Fueyo, induces p53-mediated apoptosis, the examiner does not interpret the adenoviral E1A protein as being a "mammalian restoring factor." While the specification has a broad definition of "restoring factor," and there are numerous genes which could be interpreted as being involved in the p53 apoptosis pathway, the examiner cannot provide evidence that the adenovirus vector of Fueyo satisfies this particular limitation.

Accordingly, Fueyo et al. teach all the structural limitations of the claimed vector except it lacks "a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway." According to the instant specification, p53 or a p53 derivative is an embodiment of "a mammalian restoring factor functional in restoring the p53 apoptosis pathway." Without evidence to the contrary, and reading the specification as a whole, the examiner concludes that p53 must contain the attribute recited in the instant claims directed to "whereby said restoring factor induces accelerated cell lysis and/or a faster release of virus progeny when compared to a recombinant adenovirus lacking said coding sequence."

Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19… p53 14/19 is deficient in mdm2 binding" (Results, p.5896). Lin et al. also teach that the adenovirus restores function in cells "which lack endogenous p53" (Transcriptional Activation, p. 5896) and "induce…apoptosis at similar levels to adenovirus *wt*-p53" (Transcriptional Activation, p.5896). Therefore, Lin et al. teach an adenovirus which contains a mammalian restoring factor.

Lin et al. does not teach the replication competent adenovirus, but rather a replication defective p53 adenovirus. Lin et al. also do not teach tissue specific conditional replication.

Claim 27 is directed to the adenovirus of claim 26 wherein said adenovirus is a "human adenovirus." Fueyo et al. teach "the replication-competent Δ24 virus is a human adenovirus 5" (p. 2).

Claims 30-31 are directed to the adenovirus of claim 26 wherein the genome of said adenovirus comprises "E1B-55kDa protein" (claim 30) and "E1B-19kDa protein" (claim 31). Claim 32 is directed to the adenovirus of claim 30 wherein the genome of said adenovirus comprises "genes of the…E4 region." Claim 33 is directed to the recombinant virus according to claim 30, where the virus genome comprises at least the gene encoding the adenovirus E4 or F6 protein or function analogues or derivative thereof. Claim 33 is directed to the recombinant virus according to claim 30, where the virus genome comprises at least the gene encoding the adenovirus E4 or F6 protein or function analogues or derivative thereof. Fueyo particularly teaches that only the E1A and E3 proteins are altered in their adenovirus (page 8, col.2, *Construction of the Δ24* section). Therefore, the examiner concludes Fueyo provides an adenovirus having the E1B-19kDa protein, E1B-55kDa protein, E4 protein and F6 protein, satisfying the limitations of claims 30-33.

Claim 34 is directed to the adenovirus of claim 26 wherein a mutation in a E1A region encompassing at least part of the pRb-binding CR2 domain of E1A. Fueyo et al, "constructed a tumor-selective adenovirus, Δ24, that carries a 24-bp deletion in the *E1A* region responsible for binding Rb protein." (abstract). The art indicates the pRb-binding CR2 domain of E1A is longer than 24 amino acids. Therefore, the mutant E1A region of Fueyo comprises at least part of the pRb-binding CR2 domain. The art recognizes the link between the Rb/E2F pathway and the p53 response.

Claim 35 is directed to the recombinant virus according to claim 26, wherein the restoring factor is p53 protein or a function al analogue or derivative thereof. Lin at al.

teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19… p53 14/19 is deficient in mdm2 binding" (Results, p.5896).

Claim 36 is directed to the recombinant virus according to claim 35, wherein the protein lacks a functional binding domain for a human MdM2 protein. Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19… p53 14/19 is deficient in mdm2 binding" (Results, p.5896).

Claim 37 is directed to the recombinant virus according to claim 35, wherein the protein is a function al derivative of human p53 with mutated amino acids Leu-14 and Phe-19. Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19… p53 14/19 is deficient in mdm2 binding" (Results, p.5896).

Claim 38 is directed to the adenovirus of claim 26 wherein the target cell is a human cell chosen from the group consisting of cancer cells, arthritic cells, smooth muscle cells, and cells infected with a virus. Fueyo utilize glioma cells.

Claim 39 is directed to the adenovirus of claim 27 wherein said human adenovirus is a serotype 5 adenovirus. Fueyo et al. teach "the replication-competent Δ24 virus is a human adenovirus 5" (p. 2).

Claim 40 is directed to the recombinant virus according to claim 34, wherein the mutation comprises a deletion encompassing amino acids 122-129 (LTCHEAGF) (SEQ

ID NO:5) of E1A. Fueyo et al. "constructed a tumor-selective adenovirus, Δ24, that carries a 24-bp deletion in the *E1A* region responsible for binding Rb protein." (abstract). The deletion corresponds to "amino acid residues L, T, C, H, E, A, C, and F of the E1A" (Fueyo et al., page 8). Previous Office Actions (filed 3/21/2007, page 3, lines 1-8) & Applicant's Remarks (filed 2/5/2007, page 7) resolved that the amino acid residues taught by Fueyo are, in fact LTCHEAGF.

Claim 41 is directed to the recombinant virus according to claim 26, wherein the virus genome further comprises a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof. There is nothing in Fueyo that indicates their replication competent recombinant adenovirus does not contain the adenovirus E1B-55kDa protein. The deletions within the Fueyo adenovirus are in the E1A and E3 protein. Therefore, the examiner concludes Fueyo inherently anticipates these limitations.

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to combine the tissue specific replication conditional control features of the Fueyo adenovirus with the particular p53 derivative of Lin et al. which contains mutations to the MDM-2 binding site of p53.

The person of ordinary skill in the art would have been motivated to make those modifications because both references indicate that the features of their invention offer superior properties that can be used to treat cancer. Lin et al teach "p53 14/19 modified tumor suppressor gene may be a promising therapeutic agent for human cancers that express abnormally high levels of mdm2 oncogene product" (Lin et al., abstract.

P.5895). Additionally, Fueyo et al teach "tumor-selective mutant virus seems a promising solution to the problem of gene delivery that is hindering the complete success of conventional gene therapy."

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods using adenovirus vectors having tumor-specific replication and p53 as a gene useful for inducing apoptosis in cancer cells) are taught by Fueyo or Lin and further they are taught in various combinations and are shown to be used for cancer gene therapy. It would be therefore predictably obvious to use a combination of these elements in an adenovirus vectors having tumor-specific replication in which p53 is expressed to induce apoptosis in cancer cells.

At the time the invention was made, there would have been a reasonable likelihood of success because the state of the art involving mutagenesis and adenoviruses were commonly practiced.

Therefore the adenoviruses as taught by Fueyo et al. in view of Lin et al. would have been *prima facie* obvious over the adenovirus of the instant application.

Hallenbeck & Lin

Claims 26-33, 35-39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hallenbeck et al (Human Gene Therapy. 1999; 10:1721-1733) in view of Lin et al. (Cancer Research. Oct 15, 2000. 60. p.5895-5901).

Claim 26 is directed to a replication competent recombinant adenovirus, being capable to replicate and having lytic capacity in target cells, wherein said target cells are hampered in a p53 dependent apoptosis pathway, wherein the adenovirus is a conditionally replicating adenovirus; wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells; wherein said coding sequence is operably linked to one or more expression control sequences functional in said target cells, and whereby said restoring factor induces accelerated cell lysis and/or a faster release of virus progeny when compared to a recombinant adenovirus lacking said coding sequence and wherein the virus genome further comprises a gene selected from a gene encoding the adenovirus E1B-19kDa protein or a functional analog or derivative thereof and a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof.

Hallenbeck et al. teach a tumor-specific replication-restricted adenovirus, having "the essential E1A gene…expressed from a tumor-specific promoter" (abstract). Hallenbeck teach that this vector induced tumor cell killing (page 1730, col.1, 1st parag).

The adenovirus of Hallenbeck et al. does not include a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway, as required by claim 26. Rather, Hallenbeck et al. teach that their adenovirus expresses a reporter gene.

While the specification has a broad definition of "restoring factor," and there are numerous genes which could be interpreted as being involved in the p53 apoptosis pathway, the examiner cannot provide evidence that the adenovirus vector of Hallenbeck satisfies this particular limitation.

Accordingly, Hallenbeck et al. teach all the structural limitations of the claimed vector except it lacks "a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway." According to the instant specification, p53 or a p53 derivative is an embodiment of "a mammalian restoring factor functional in restoring the p53 apoptosis pathway." Without evidence to the contrary, and reading the specification as a whole, the examiner concludes that p53 must contain the attribute recited in the instant claims directed to "whereby said restoring factor induces accelerated cell lysis and/or a faster release of virus progeny when compared to a recombinant adenovirus lacking said coding sequence."

Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19… p53 14/19 is deficient in mdm2 binding" (Results, p.5896). Lin et al. also teach that the adenovirus restores function in cells "which lack endogenous p53" (Transcriptional Activation, p. 5896) and

"induce…apoptosis at similar levels to adenovirus *wt*-p53" (Transcriptional Activation, p.5896). Therefore, Lin et al. teach an adenovirus which contains a restoring factor.

Lin et al. does not teach the replication competent adenovirus, but rather a replication defective p53 adenovirus. Lin et al. also do not teach tissue specific conditional replication.

Claim 27 is directed to the adenovirus of claim 26 wherein said adenovirus is a "human adenovirus." Hallenbeck et al. teach human adenovirus 5" (Materials).

Claim 28 is directed to the recombinant virus according to claim 26, wherein expression of at least one essential early adenovirus gene is controlled by a tumor specific promoter. Hallenbeck et al. teach a tumor-specific replication-restricted adenovirus, having "the essential E1A gene…expressed from a tumor-specific promoter" (abstract).

Claim 29 is directed to the recombinant virus according to claim 26, wherein the adenovirus is a heterologously trans-complemented adenovirus. The specification uses a definition of "heterologously trans-complemented adenovirus" which is different from the usual meaning in the art. The specification teaches, "In a first type of replication competent recombinant adenovirus said parts that are essential for at least one step of the adenovirus infectious life cycle are also removed, but the essential functions of said parts are complemented by inserting functional expression cassettes for heterologous proteins that provide said essential functions in the recombinant adenovirus genome. This type of recombinant adenovirus is referred to herein as a heterologously trans-complemented adenovirus, and therefore is to be regarded as replication competent

according to the definition presented herein." (page 3, lines 3-12). In the adenovirus described by Hallenbeck, the E1a gene was removed from the adenovirus and replaced by inserting an alphafetoprotein promoter-E1a cassette which provided the essential function (Fig.1, and page 1722, *Construction of HCC-specific replication-restricted adenoviral vector* section). By the definition provided by the instant specification, the resulting adenovirus of Hallenbeck is a heterologously trans-complemented adenovirus.

Claims 30-31 are directed to the adenovirus of claim 26 wherein the genome of said adenovirus comprises "E1B-55kDa protein" (claim 30) and "E1B-19kDa protein" (claim 31). Claim 32 is directed to the adenovirus of claim 30 wherein the genome of said adenovirus comprises "genes of the…E4 region." Claim 33 is directed to the recombinant virus according to claim 30, where the virus genome comprises at least the gene encoding the adenovirus E4 or F6 protein or function analogues or derivative thereof. Claim 33 is directed to the recombinant virus according to claim 30, where the virus genome comprises at least the gene encoding the adenovirus E4 or F6 protein or function analogues or derivative thereof. Hallenbeck particularly teaches that only the E1A protein is altered in their adenovirus. Therefore, the examiner concludes Hallenbeck provides an adenovirus having the E1B-19kDa protein, E1B-55kDa protein, E4 protein and F6 protein, satisfying the limitations of claims 30-33.

Claim 35 is directed to the recombinant virus according to claim 26, wherein the restoring factor is p53 protein or a function al analogue or derivative thereof. Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino

acid residues Leu-14 and Phe-19… p53 14/19 is deficient in mdm2 binding" (Results, p.5896).

Claim 36 is directed to the recombinant virus according to claim 35, wherein the protein lacks a functional binding domain for a human MdM2 protein. Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19… p53 14/19 is deficient in mdm2 binding" (Results, p.5896).

Claim 37 is directed to the recombinant virus according to claim 35, wherein the protein is a function al derivative of human p53 with mutated amino acids Leu-14 and Phe-19. Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19… p53 14/19 is deficient in mdm2 binding" (Results, p.5896).

Claim 38 is directed to the adenovirus of claim 26 wherein the target cell is a human cell chosen from the group consisting of cancer cells, arthritic cells, smooth muscle cells, and cells infected with a virus. Hallenbeck utilize hepatocellular carcinoma cells.

Claim 39 is directed to the adenovirus of claim 27 wherein said human adenovirus is a serotype 5 adenovirus. Hallenbeck et al. teach that their adenovirus is a human adenovirus 5 (Materials).

Claim 41 is directed to the recombinant virus according to claim 26, wherein the virus genome further comprises a gene encoding the adenovirus E1B-55kDa protein or

a functional analog or derivative thereof. There is nothing in Hallenbeck that indicates their replication competent recombinant adenovirus does not contain the adenovirus E1B-55kDa protein. The deletions within the Hallenbeck adenovirus are in the E1A protein. Therefore, the examiner concludes Hallenbeck teaches these limitations.

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to incorporate the tissue specific replication conditional control features of the Hallenbeck adenovirus with the particular p53 derivative of Lin et al. which contains mutations to the MDM-2 binding site of p53.

The person of ordinary skill in the art would have been motivated to make those modifications because both references indicate that the features of their invention offer superior properties that can be used to treat cancer. Lin et al teach "p53 14/19 modified tumor suppressor gene may be a promising therapeutic agent for human cancers that express abnormally high levels of mdm2 oncogene product" (Lin et al., abstract. P.5895). Additionally, Hallenbeck et al. teach "the strategy of utilizing tumor-specific replication-restricted vector for cancer therapy has many advantages over utilized cancer gene therapy protocols" (page 1731, col.2).

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods using adenovirus vectors having tumor-

specific replication and p53 as gene useful for inducing apoptosis in cancer cells) are taught by Hallenbeck or Lin and further they are taught in various combinations and are shown to be used for cancer gene therapy. It would be therefore predictably obvious to use a combination of these elements in an adenovirus vectors having tumor-specific replication in which p53 is expressed to induce apoptosis in cancer cells.

At the time the invention was made, there would have been a reasonable likelihood of success because the state of the art involving mutagenesis and adenoviruses were commonly practiced.

Therefore the adenoviruses as taught by Hallenbeck et al. in view of Lin et al. would have been *prima facie* obvious over the adenovirus of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633